Neuroendocrine Deregulation of Food Intake, Adipose Tissue and the Gastrointestinal System in Obesity and Metabolic Syndrome

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Abstract

Obesity is an excess of fat mass. Fat mass is an energy depot but also an endocrine organ. A deregulation of the sympathetic nervous system (SNS) might produce obesity. Stress exaggerates diet-induced obesity. After stress, SNS fibers release neuropeptide Y (NPY) which directly increases visceral fat mass producing a metabolic syndrome (MbS)-like phenotype. Adrenergic receptors are the main regulators of lipolysis. In severe obesity, we demonstrated that the adrenergic receptor subtypes are differentially expressed in different fat depots. Liver and visceral fat share a common sympathetic pathway, which might explain the low-grade inflammation which simultaneously occurs in liver and fat of the obese with MbS. The neuroendocrine melanocortinergic system and gastric ghrelin are also greatly deregulated in obesity. A specific mutation in the type 4 melanocortin receptor induces early obesity onset, hyperphagia and insulin-resistance. Nonetheless, it was recently discovered that a mutation in the prohormone convertase 1/3 simultaneously produces severe gastrointestinal dysfunctions and obesity.

Key words

Obesity – sympathetic nervous system – metabolic syndrome – adrenergic receptors – prohormone convertase 1/3 – type 4 melanocortin receptor

Abbreviations

AgRP: agouti-related peptide; ANP: atrial natriuretic peptide; AR: adrenergic receptors; BMI: body mass index; CART: cocaine- and amphetamine-regulated transcript; FF A: free fatty acids; GH: growth hormone; HSAT: human subcutaneous adipose tissue; HVAT: human visceral adipose tissue; MbS: metabolic syndrome; MC3R: type 3 melanocortin receptor; MC4R: type 4 melanocortin receptor; NPY: neuropeptide Y; NPY2: type 2 NPY receptor; PAI-1: plasminogen activator inhibitor factor1; PC 1/3: prohormone convertase 1/3; POMC: pro-opiomelanocortin; TNF: tumor necrosis factor; UCP1: uncoupling protein 1.

Introduction

The term neuroendocrinology is referred to the interactions existing between the nervous system and the endocrine glands of the body. At the beginning of the previous century, Geoffrey Harris made the first discovery in this domain showing that the mammalian hypophysis was regulated by factors secreted by neurons of the hypothalamus in the hypothalamo-hypophysial portal circulation. Appetite and energy balance are regulated by several neuroendocrine circuits. If a deregulation of energy balance occurs, body fat mass increases. Adipose tissue is the major energy storage compartment in higher eukaryotes. However, in the last years it acquired the dignity of an endocrine organ, because it was discovered to synthesize and release molecules (adipocytokines) playing endocrine, autocrine or paracrine roles. Obesity is an excess of body fat mass. Central obesity and the metabolic syndrome (MbS) are pathological conditions characterized by an increase in truncal body fat mass associated with a chronic low-grade inflammatory state. This inflammatory state is mainly due to the imbalance between pro-inflammatory and anti-inflammatory cytokines produced by both adipocytes and macrophages infiltrating not only adipose tissue, but also liver and muscles. Energy homeostasis depends on the balance existing between adipose tissue and some neuroendocrine and mitochondrial systems [the sympathetic nervous system, the melanocortinergic system (involving leptin), the ghrelin-neuropeptide Y (NPY) system, the serotonin and cocaine- and amphetamine-regulated transcript (CART) system, the uncoupling proteins] [1-3]. Some of these pathways directly influence body fat mass; others play a role in the central regulation of energy balance whose last target is body fat mass. This review will mainly focus on the dysfunctions in the above mentioned
Biology of adipose tissue in obesity phenotypes and metabolic syndrome

To understand the role played by adipose tissue in body weight disorders, the histology and biology of adipose tissue deserve major attention. From the histological point of view, human body fat is mainly represented by unilocular adipocytes. Obesity is defined as an increase in total fat mass and it occurs when unilocular adipocytes increase their number (hyperplasia) or size (hypertrophy) following macrophage infiltration of fat tissue. On the basis of the body mass index (BMI), which represents the ratio between the body weight (kg) and the square of height (m), different classes of weight disorders have been identified (NIH Consensus Development Conference Statement 1992) ranging from overweight (BMI>25 kg/m2) to morbid obesity (BMI>40 kg/m2). From the biological point of view, unilocular adipocytes, also known as white adipocytes, are the most abundant cell type in mammalian fat. Unilocular adipocytes are the major energy storage compartment in higher eukaryotes. They store energy as triglycerides in periods of body energy excess and mobilize it in periods of energy defect (fasting) or energy demand (exercise).

From the energetic point of view, an increase in total fat mass takes place only when an impaired balance between energy intake and energy expenditure occurs which is followed by an increased size (hypertrophy) of already existing adipocytes. In addition to unilocular adipocytes, multilocular adipocytes have also been found in mammals. They represent a completely different cell type (brown adipocytes) expressing a mitochondrial protein, uncoupling protein 1 (UCP1) mainly devoted to dissipate energy as heat (thermogenesis). UCP1-positive multilocular adipocytes are mainly represented in human retroperitoneal adipose tissue depots [2, 3]. In both human and animal obesity, excess fat mass is never due to an increased number or size of UCP1-positive adipocytes.

In the most severe form of obesity, morbid obesity, increased number (hyperplasia) and size (hypertrophy) of unilocular adipocytes coexist. To explain the occurrence of morbid obesity it has been postulated that hyperplastic adipocytes release paracrine factors (prostacyclin, angiotensinogen) which stimulate the differentiation of precursor cells into mature adipocytes. However, hyperplasia might also be due to reduced expression and secretion of factors inhibiting adipocytes differentiation and growth.

In the last years adipocytes have acquired the dignity of endocrine cells, because it was discovered that they synthesize and release proteins playing endocrine, autocrine or paracrine roles [4-9] (Table 1). In Table I and Figure 1 we report some of the most important secretory products of adipocytes. Leptin was the first secretory protein discovered in adipocytes. In animal models, leptin displays central and peripheral effects important in regulating not only satiety but also fertility [10]. Leptin is a hormone mainly, but not exclusively, secreted by adipocytes whose receptors are spread out in different peripheral organs, including the ovary. Surprisingly, human homozygotes, for a point mutation of the ob gene, display a phenotype having as main features morbid obesity, MbS and reduced fertility [11]. Adiponectin and resistin are secretory products of adipocytes too. Adiponectin levels are inversely related to insulin resistance. Resistin is a marker of the cardiovascular risk [4-9]. We recently demonstrated that atrial natriuretic peptide (ANP) is expressed and secreted by human pre-adipocytes [4]. Atrial natriuretic peptide is not only a strong hypotensive compound, but also a lipolytic compound [4].

Fat distribution has a major role in human diseases. Upper body obesity represents one of the main phenotypic features of a polygenic syndrome defined as Metabolic Syndrome (MBs), characterized by a pro-thrombotic state associated with impaired fasting glucose and/or arterial hypertension and/or dyslipidemia [12, 13]. Insulin-resistant individuals commonly have an abnormal fat distribution which is predominant in the upper part of the body. Accumulation of fat in the upper part of the body can occur either intraperitoneally or retro-peritoneally or subcutaneously. However, excess intra-peritoneal fat is more strongly associated with insulin resistance and type 2 diabetes than subcutaneous or retroperitoneal adipose tissue depots [14-18]. Free fatty acids (FFA) produced by the intraperitoneal fat cross portal circulation and become a direct source of FFA for liver. In obese subjects with increased visceral fat mass, there is an enormous amount of FA which reaches the liver and accounts for a decrease in glucose oxidation.

<table>
<thead>
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<th>Factors</th>
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</tr>
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</tr>
<tr>
<td>Angiotensinogen</td>
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</tr>
<tr>
<td>ANP</td>
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<td>+</td>
</tr>
<tr>
<td>Cholesteryl-ester transferase</td>
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<tr>
<td>Estrogens</td>
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<tr>
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<tr>
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<tr>
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</tr>
<tr>
<td>Tumor necrosis factor-α</td>
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<td>Visfatin</td>
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Neuroendocrine control of fat mass in obesity

The main pathways regulating lipolysis involve adrenergic receptors, atrial natriuretic peptide receptors and insulin receptors. The cascade of events following the stimulation of atrial natriuretic peptide receptor, insulin receptor and adrenergic receptors are reported [3-4]. Free fatty acids and glycerol are the final products of lipolysis. Blue arrows indicate inhibitory pathways, red arrows stimulating pathways. Adipocytes are endocrine cells producing hormones and adipokines [3-8]. Some secretory products of adipocytes are leptin, adiponectin, resistin, atrial natriuretic peptide, tumor necrosis factor α. An extensive list of adipocyte-produced factors is reported in Table 1.

Abbrev: AC: adenylate cyclase; ANP: atrial natriuretic peptide; AR, adrenergic receptors; ATGL, adipose triglycerides lipase; cAMP, cyclic AMP; cGK,: cGMP-dependent protein kinase; cGMP: cyclic guanosine monophosphate; FFA, free fatty acids; HSL, hormone-sensitive lipase; IP3, inositol triphosphate; IR: insulin receptor; IRS, insulin receptor substrate; PDE-3B, fosphodiesterase 3B; Peri A, perilipin; PI3K, phosphoinositide-3 kinase; PKA: protein kinase A; PKB: protein kinase B; TGL, triglycerides; TNFα, tumor necrosis factor α

Sympathetic nervous system and adipose tissue

Adrenergic receptor (AR) dysregulation might play a role in the occurrence of human obesity. It was indeed demonstrated that in white obese women, some β₂AR polymorphisms are associated with changes in adiposity phenotype [19]. Nonetheless in white obese men, β₂AR polymorphisms are associated with the occurrence of the MbS [20]. In addition, a strong relationship between β₂AR gene haplotypes and adipocyte lipolysis has been found in women [21]. In overweight women, three homozygous haplotypes were found that differed in β₂AR sensitivity and in maximal catecholamine-induced lipolysis. These haplotypes might be important genetic factors behind impaired lipolysis in obesity [21].

The adrenergic receptors are spread out either in the brainstem or in peripheral organs (Fig. 2). As far as the distribution of ARs in adipose tissue depots is concerned, previous studies reported that in both normalweight and overweight subjects, the distribution of different AR subtypes differs in subcutaneous adipose tissue (HSAT) as compared with visceral adipose tissue (HVAT). In humans, fat mass is mainly controlled through the balance between the lipolytic and the anti-lipolytic ARs. Most studies have been performed measuring receptor density or receptor-mediated lipolysis. On the basis of these studies, it has been commonly accepted that the β-ARs stimulate lipolysis whereas the α-ARs inhibit lipolysis. As far as the ARs are concerned, only α₂A-AR plays an unequivocal anti-lipolytic role [22]. The α₂AR is also involved in the estrogen-mediated anti-lipolytic effect, since estrogens up-regulate α₂A-AR through binding to the estrogen receptor A [23]. In the majority of the studies, β-receptor density and lipolysis were both higher in HVAT than in HSAT [22]. In a recent study, we analysed the expression of several AR subtypes in HVAT and HSAT of morbid obese subjects. Our data confirm that the expression of α₂A-AR is higher in HSAT than in HVAT. However β₂AR
Diagnostic criteria for the Metabolic Syndrome

<table>
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</tr>
<tr>
<td></td>
<td>Female</td>
<td>≥88</td>
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OR (according to IDF**)

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<tr>
<td></td>
<td>Female</td>
<td>≥80</td>
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<tr>
<td>South Asians, Chinese</td>
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</tr>
<tr>
<td></td>
<td>Female</td>
<td>≥80</td>
</tr>
<tr>
<td>Japanese</td>
<td>Male</td>
<td>≥885</td>
</tr>
<tr>
<td></td>
<td>Female</td>
<td>≥90</td>
</tr>
</tbody>
</table>

1. **Central obesity**

2. Elevated triglyceridemia (≥ 150 mg/dl)
3. Decreased HDL cholesterolemia (< 40 mg/dl in males, < 50 mg/dl in females)
4. Elevated arterial blood pressure (≥130/85 mmHg)
5. Elevated fasting blood glucose (≥ 110 mg/dl)


been known to exaggerate diet-induced obesity, but only recently it was discovered that stress increases the release of NPY from sympathetic nerves and directly stimulates NPY2 receptors (NPY2R) in visceral fat upregulating NPY2R in a glucocorticoid-dependent manner. The final effect is an increase in abdominal fat and a MbS-like phenotype. NPY2R antagonists play an anti-angiogenic and anti-adipogenic role.
Central control of feeding and fat mass in α1B-AR knock-out mice. In mice lacking of α1B-AR the activity of the parasympathetic nervous system is increased leading to increased insulin secretion, hepatic glycogen stores and insulin resistance. Hypothalamic Neuropeptide Y and Agouti-related peptide mRNA levels increase despite of hyperleptinemia. Under high-fat feeding body fat mass increases and a Metabolic Syndrome-like phenotype develops. Blue signs indicate inhibitory pathways, red signs stimulating pathways. Abbrev: AgRP, Agouti-related peptide; MC4R: type 4 melanocortin receptor; MSH, melanocyte stimulating hormone; NPY, neuropeptide Y.

and might represent a potential treatment for central obesity and MbS [28].

Melanocortinergic system, body fat mass and gastrointestinal system

There are several lines of evidence that the melanocortinergic system is involved in feeding behavior and energy expenditure and that the central melanocortin system is a key mediator of the catabolic effects of insulin in the brain [29-31]. The melanocortins are post-translational products of the pro-opiomelanocortin (POMC) prohormone. Melanocortins not only play a crucial role in energy balance but also in pigmentation, inflammation, memory and/or learning, thermoregulation, analgesia, depression, and stress responses [31]. The type 4 melanocortin receptor (MC4R) is one of the G-protein coupled receptors selective for melanocortins. It is mainly expressed in the brain and is involved in mood control and feeding behaviour [32].

Both appetite and energy expenditure depend on the insulin/leptin-arcuate nucleus axis of the hypothalamus. Specific receptors for insulin and leptin are expressed in the arcuate nucleus. Leptin interacts with MC3/4R to reduce feeding and increase thermogenesis by activating the sympathetic nervous system. Leptin down-regulates NPY, AgRP, orexins, and melanocyte-stimulating hormone in the hypothalamus. In the presence of low circulating levels of leptin, the above mentioned hormones stimulate food intake. Ghrelin is another hormone connecting the peripheral energy storage compartments and central nuclei controlling feeding. Gastric secretion of ghrelin increases during fasting and stimulates the release of growth hormone (GH), NPY and AgRP. The GH is stimulating lipolysis. By contrast, NPY and AgRP are anabolic hormones increasing feeding and energy efficiency. The melanocortinergic system has been extensively studied in genetic animal models of obesity. The agouti mice, termed agouti for their yellow coat color, are obese and show a mutation in MC4R. In humans, specific mutations in MC4R result in a distinct obesity syndrome that is inherited in a codominant manner and was first discovered in a cohort of children who had red hair, early obesity onset, hyperphagia and insulin-resistance [32].

Several studies deepen the interaction existing between neuroendocrine systems, adipose tissue and gastrointestinal system in obesity, since the latter plays a fundamental role in processing nutrients [1, 33]. Very recently a congenital deficiency of the prohormone convertase (PC) 1/3 which cleaves POMC, AgRP, cholecystokinin, pro-glucagon, glucagon-like peptide-1 and pro-insulin has been demonstrated to lead to a syndrome characterized by obesity, small intestinal dysfunction, hyperphagia and dysregulation of glucose homeostasis [34]. Interestingly, all the above mentioned hormones are strong inhibitors of food intake. The clinical picture is characterized by a
neonatal onset enteropathy and intractable diarrhea which coexist with a selective malabsorption for monosaccharides and aminoacids. GLP-1 and GLP-2 are equimolarly produced in intestinal L-cells and it might be argued that the impaired metabolism and secretion of GLP-2 is responsible for the enteropathy. Enteroendocrine cells play an important role in the intestinal absorption. This syndrome is the first example of a monogenic defect which simultaneously produces obesity, diarrhea and malabsorption.

A more extensive knowledge of the neuroendocrine mechanisms involved in genetic forms of severe obesity and gastrointestinal dysfunctions might help to develop new therapeutic strategies to separately treat increased fat mass and hyperphagia which are often, but not always coexisting in human obesity and the metabolic syndrome.

References